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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/977,787	11/25/1997	LEE MIZZEN	STS96-02A	3496

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EXAMINER	
ZEMAN, MARY K	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/977,787	MIZZEN ET AL.	
	Examiner	Art Unit	
	Mary K Zeman	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,57-59,61-64,66,68,69,88,89 and 91-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54,57-59,61-64,66,68,69,88,89 and 91-98* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The indicated allowability of claims 54, 57, 58, 66, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, 93 is withdrawn in view of the newly discovered reference(s) to Johansson et al. (1990). Rejections based on the newly cited reference(s) follow.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young in view of Johannson et al. (1990).

The claims are drawn to fusion proteins comprising stress proteins and influenza proteins, and their use in methods of inducing immune responses against an influenza antigen. The influenza antigens comprise NP, NA, M1, M2, PB1, PB2 or PA. The stress proteins can be of bacterial origin. The fusion protein can elicit a variety of immune responses.

Young (WO 94/29459, PTO-1449 AL2) discloses fusion proteins of bacterial stress proteins with antigens, proteins or peptides. The heat shock proteins can be bacterial, specifically from mycobacteria. Specific antigens disclosed by Young include hsp60, hsp65, hsp70, etc. Young notes that heat shock proteins are known in the art to induce T-cell mediated immune responses when administered to a subject. At pages 21-22, Young specifies that the heat shock protein can be produced recombinantly, and specifically that it can be produced recombinantly in fusion with an antigen. The antigens, proteins and/or peptides can be selected from viruses, pathogens, neoplasias "any substance against which an immune response is desired." Young exemplifies a fusion protein between hsp70 and HIV p24 antigen. This fusion protein (in combination with an acceptable diluent or buffer) was shown to induce a humoral response to the viral antigen that was more than 2 fold greater than compared to the viral antigen

alone, and clearly induced a T cell response to the viral antigen. Young does not specifically disclose influenza antigens.

Johansson et al. (J infectious disease 1990 vol. 162, pages 800-809.) disclose purified neuraminidase vaccines for the induction of an immune response to the influenza virus. Johansson provides purified NA antigens for inoculation, and tests with viral challenge. The inoculation of the subjects with the NA vaccine results in the generation of a strong humoral response (antibodies to NA). The purified NA had superior NA immunogenicity in comparison to the whole virus vaccine.

It would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza NA antigen of Johansson et al. One of skill in the art would have been motivated to make such a change in order to provoke a response from both the humoral immune system, and the cellular immune system. The most effective vaccines activate both parts of the immune system. Young discloses that the heat shock protein induces a clear T cell response to the antigen that is in fusion, and Johansson et al. disclose that influenza NA antigen can provoke a strong, humoral immune system response. One of skill in the art would have had a reasonable expectation of success in making the fusion construct between hsp70 and the influenza NA, as only routine cloning skill are required. Young provides the necessary hsp sequences and vectors, and Johansson et al. provide the influenza NA. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young in view of Fiers et al. (USP 5,962,298 or WO 95/18861).

Young (WO 94/29459, PTO-1449 AL2) discloses fusion proteins of bacterial stress proteins with antigens, proteins or peptides. The heat shock proteins can be bacterial, specifically from mycobacteria. Specific antigens disclosed by Young include hsp60, hsp65, hsp70, etc. Young notes that heat shock proteins are known in the art to induce T-cell mediated immune responses when administered to a subject. At pages 21-22, Young specifies that the

heat shock protein can be produced recombinantly, and specifically that it can be produced recombinantly in fusion with an antigen. The antigens, proteins and/or peptides can be selected from viruses, pathogens, neoplasias "any substance against which an immune response is desired." Young exemplifies a fusion protein between hsp70 and HIV p24 antigen. This fusion protein (in combination with an acceptable diluent or buffer) was shown to induce a humoral response to the viral antigen that was more than 2 fold greater than compared to the viral antigen alone, and clearly induced a T cell response to the viral antigen. Young does not specifically disclose influenza antigens.

Fiers et al. (US 5,962,298, having a 102(e) date of 9/27/96; WO 95/18861 is the WO Equivalent, having a publication date of 7/13/1995) disclose purified neuraminidase vaccines for the induction of an immune response to the influenza virus. Fiers provides purified recombinant NA antigens for use as a vaccine. The inoculation of the subjects with the NA vaccine results in the generation of a strong humoral response (antibodies to NA), and protection against homologous challenge. The NA vaccine also provided strong partial protection to heterologous challenge. Passive transfer of serum from NA inoculated mice was also protective, indicating the bulk of the protective response was due to circulating antibodies to NA.

It would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza NA antigen of Fiers et al. One of skill in the art would have been motivated to make such a change in order to provoke a response from both the humoral immune system, and the cellular immune system. The most effective vaccines activate both parts of the immune system. Young discloses that the heat shock protein induces a clear T cell response to the antigen that is in fusion, and Fiers et al. disclose that influenza NA antigen can provoke a strong, humoral immune system response. One of skill in the art would have had a reasonable expectation of success in making the fusion construct between hsp70 and the influenza NA, as only routine cloning skill are required. Young provides the necessary hsp sequences and vectors, and Fiers et al. provide the influenza NA sequences, and show that recombinant NA is effective at provoking an immune response . Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 54, 57, 58, 66, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young in view of Paoletti et al. (USP 5,174,993).

Young (WO 94/29459, PTO-1449 AL2) discloses fusion proteins of bacterial stress proteins with antigens, proteins or peptides. The heat shock proteins can be bacterial, specifically from mycobacteria. Specific antigens disclosed by Young include hsp60, hsp65, hsp70, etc. Young notes that heat shock proteins are known in the art to induce T-cell mediated immune responses when administered to a subject. At pages 21-22, Young specifies that the heat shock protein can be produced recombinantly, and specifically that it can be produced recombinantly in fusion with an antigen. The antigens, proteins and/or peptides can be selected from viruses, pathogens, neoplasias "any substance against which an immune response is desired." Young exemplifies a fusion protein between hsp70 and HIV p24 antigen. This fusion protein (in combination with an acceptable diluent or buffer) was shown to induce a humoral response to the viral antigen that was more than 2 fold greater than compared to the viral antigen alone, and clearly induced a T cell response to the viral antigen. Young does not specifically disclose influenza antigens.

Paoletti et al. (US 5,174,993) disclose recombinant vectors comprising nucleoprotein (NP) for use in producing an immunological response. Paoletti provides recombinant avipox vectrs which can comprise chicken nucleoprotein gene (col. 6) (among many others, including HA) which produce NA antigens for use as a vaccine. The vector used to clone the NP gene is called pNP33. The inoculation of the subjects with the avipox vaccine results in the generation of a strong humoral response, and protection against homologous challenge.

It would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza NP antigen of Paoletti et al. One of skill in the art would have been motivated to make such a change in order to provoke a response from both the humoral immune system, and the cellular immune system. The most effective vaccines activate both parts of the immune system. Young discloses that the heat shock protein induces a clear T cell response to the antigen that is in fusion, and Paoletti et al. disclose that influenza NP antigen can provoke a strong, humoral immune system response. One of skill

in the art would have had a reasonable expectation of success in making the fusion construct between hsp70 and the influenza NP, as only routine cloning skill are required. Young provides the necessary hsp sequences and vectors, and Paoletti et al. provide the influenza NP sequences,. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young in view of Kendal et al (USP 5,290,686).

Young (WO 94/29459, PTO-1449 AL2) discloses fusion proteins of bacterial stress proteins with antigens, proteins or peptides. The heat shock proteins can be bacterial, specifically from mycobacteria. Specific antigens disclosed by Young include hsp60, hsp65, hsp70, etc. Young notes that heat shock proteins are known in the art to induce T-cell mediated immune responses when administered to a subject. At pages 21-22, Young specifies that the heat shock protein can be produced recombinantly, and specifically that it can be produced recombinantly in fusion with an antigen. The antigens, proteins and/or peptides can be selected from viruses, pathogens, neoplasias "any substance against which an immune response is desired." Young exemplifies a fusion protein between hsp70 and HIV p24 antigen. This fusion protein (in combination with an acceptable diluent or buffer) was shown to induce a humoral response to the viral antigen that was more than 2 fold greater than compared to the viral antigen alone, and clearly induced a T cell response to the viral antigen. Young does not specifically disclose influenza antigens.

Kendal et al. (US 5,290,686) disclose recombinantly expressed influenza M2 proteins for the induction of an immune response to the influenza virus. Kendal provides baculovirus expressed M2 antigens, and indicates that the M2 protein is a target of the immune system in influenza infection. The M2 protein has a lower rate of antigenic drift than other influenza proteins, and is therefore a good candidate for use in vaccines. Kendal notes that mice inoculated with monoclonal antibodies to M2 were partially protected against viral challenge.

Infected human sera also produces antibodies to M2, indicating that M2 antigens provoke the humoral immune system.

It would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza M2 antigen of Kendal et al. One of skill in the art would have been motivated to make such a change in order to provoke a response from both the humoral immune system, and the cellular immune system. The most effective vaccines activate both parts of the immune system. Young discloses that the heat shock protein induces a clear T cell response to the antigen that is in fusion, and Kendal et al. disclose that influenza M2 antigen can provoke a strong, humoral immune system response. One of skill in the art would have had a reasonable expectation of success in making the fusion construct between hsp70 and the influenza M2, as only routine cloning skill are required. Young provides the necessary hsp sequences and vectors, and Kendal et al. provide the influenza M2 sequences, and show that recombinant M2 is effective at provoking an immune response . Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young in view of Parkin et al. (USP 5,690,937).

Young (WO 94/29459, PTO-1449 AL2) discloses fusion proteins of bacterial stress proteins with antigens, proteins or peptides. The heat shock proteins can be bacterial, specifically from mycobacteria. Specific antigens disclosed by Young include hsp60, hsp65, hsp70, etc. Young notes that heat shock proteins are known in the art to induce T-cell mediated immune responses when administered to a subject. At pages 21-22, Young specifies that the heat shock protein can be produced recombinantly, and specifically that it can be produced recombinantly in fusion with an antigen. The antigens, proteins and/or peptides can be selected from viruses, pathogens, neoplasias "any substance against which an immune response is desired." Young exemplifies a fusion protein between hsp70 and HIV p24 antigen. This fusion protein (in combination with an acceptable diluent or buffer) was shown to induce a humoral

response to the viral antigen that was more than 2 fold greater than compared to the viral antigen alone, and clearly induced a T cell response to the viral antigen. Young does not specifically disclose influenza antigens.

Parkin et al. (US 5,690,937) disclose recombinant PB2 antigens for the induction of an immune response to the influenza virus. Parkin et al also disclose PB1, PA and NP genes of influenza and note their importance in infection, and resulting attraction as a vaccine. Parkin provides the sequences of the PB2 gene, as well as a variety of temperature sensitive mutations of the PB2 gene. M and NP sequences are also disclosed. Routine cloning methods are used to produce recombinant PB2 proteins. Recombinant viruses comprising the variously described proteins are to be used as vaccines.

It would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza PB2 antigen of Parkin et al. One of skill in the art would have been motivated to make such a change in order to provoke a response from both the humoral immune system, and the cellular immune system. The most effective vaccines activate both parts of the immune system. Young discloses that the heat shock protein induces a clear T cell response to the antigen that is in fusion, and Parkin et al. disclose that influenza PB2 antigen can provoke a humoral immune system response. One of skill in the art would have had a reasonable expectation of success in making the fusion construct between hsp70 and the influenza PB2, as only routine cloning skill are required. Young provides the necessary hsp sequences and vectors, and Parkin et al. provide the influenza PB1, Pb2, NP, Na and M sequences. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Rota et al. also discloses recombinant NP sequences and their antigenicity. (US 5,316,910).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (571) 272 0723

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P Woodward can be reached on (571) 272 0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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MARY K. ZEMAN
PRIMARY EXAMINER
AU 1631 10/22/04